PATENT
Customer No. 22,852
Attorney Docket No. 04012.0384

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of:	)	
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Lukas-Laskey et al.	)	Group Art Unit: 1614
	)	
Application No. 10/721,022	)	Examiner: P. Spivack
	)	
Original Patent No. 5,902,821	)	
	)	
Original Issue Date: May 11, 1999	)	
	)	
Reissue Filed: November 25, 2003	)	
	)	
For: USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE

The Office Action dated January 11, 2005, has been received and its contents carefully considered.

I. Reissue Declaration

The Reissue Declaration filed with this application is characterized by the Office as being defective because "[t]he error recited would only be a semantic altering of the wording already in the preamble." (Office Action, pg. 3.) Applicants respectfully disagree with the rejection of the Reissue Declaration.

First, as recognized in the MPEP, a preamble may be non-limiting in some cases. (MPEP § 2111.02.) The preamble has been expressly given no weight in some

method of treatment claims. *See, e.g., Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1373, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001). Accordingly, to the extent that claims in the original patent *could* be interpreted such that the preamble is not a limitation, the cited error is not merely a semantic alteration. Therefore, while Applicants would not agree with a construction of the original claims giving no weight to the preamble, the Reissue Declaration's cited error and the amendment to the body of the claims to correct for the possibility of a construction giving no weight to the preamble is submitted to be an error within the meaning of 35 U.S.C. § 251 and 37 CFR § 1.175.

Second, the body of the claim does not merely repeat the preamble. The preamble recites:

> A method of decreasing mortality caused by congestive heart failure in a patient in need of such decrease, said method comprising. . . .

As is evident, in the preamble no specific aspect of the method is directly correlated with mortality reduction. Although the phrase "to decrease a risk of mortality caused by congestive heart failure" used in the body is similar to wording in the preamble, in context the amended claim reads:

> administering to said patient third dosages daily for a maintenance period to decrease a risk of mortality caused by congestive heart failure. . . .

Thus, as recited in the body of the amended claim, the method comprises administering a third dosage daily for a maintenance period to decrease a risk of mortality caused by CHF. This recitation, with the connection between the third dosage and the maintenance period, is not merely a semantic alteration of the preamble.

For at least the foregoing reasons, reconsideration and acceptance of the Reissue Declaration are respectfully requested.

In addition, Applicants note with appreciation the Office's suggestion that "[s]ince mortality is absolute, Applicants may consider claim language directed to reducing the occurrence of mortality from congestive heart failure." (Office Action, pg. 3.) However, Applicants respectfully elect not to further amend the claims at this time.

Finally, the Office notes an error in the Reissue Declaration concerning the filing date of the foreign priority application, DE 195 03 995. (Office Action, pg. 3.) The Application Transmittal sheet for this application properly identifies the filing date of DE 195 03 995 as February 8, 1995. The Office has also acknowledged the claim for priority under 35 U.S.C. §119 and receipt of certified copies of the priority document in parent application 08/875,506. (Office Action, pg. 2.) However, the Reissue Declaration erroneously refers to the filing date of DE 195 03 995 as February 8, 1985. An Application Data Sheet is being filed herewith to correct and clarify the discrepancy.

II. Information Disclosure Statement

Prior to the Office Action dated January 11, 2005, Applicants filed an Information Disclosure Statement ("IDS") on December 28, 2004. However, the IDS was not acknowledged in the January 11, 2005, Office Action. Applicants respectfully request that the Office consider the IDS and listed documents, and indicate that they were considered by making appropriate notations on the forms provided with the IDS.

III. Rejection under 35 U.S.C. § 112

Claims 1-30 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled for the stated reason that:

> the specification . . . does not reasonably provide enablement for 'said maintenance period is greater than six months' in relation to the administration of the third dosages. The specification does not enable any person skilled in the

> art . . . to practice the invention commensurate in scope with these claims.

(Office Action, pg. 3.) The Office does recognize that "[i]n column 5 a maintenance dose is set forth" and "[i]n column 7, lines 56-67 a six to twelve month maintenance period is given," but expresses concern that the maintenance period "is not directly related to the maintenance dose." (*Id.*) Applicants respectfully traverse.[1]

First, the standard for enablement is that while the specification must enable the full scope of the claimed invention "[t]hat is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art." *AK Steel Corp. v. Sollac*, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003) (citations omitted). MPEP § 2164.01 In the present case, there is no dispute that the specification provides for both a "maintenance dose" and a "maintenance phase." The only concern raised by the Office is the directness of the relationship between the maintenance dose and period. In response, Applicants respectfully submit that it is within the level of skill in the art, based on the disclosed maintenance dose and maintenance period, to provide

[1] The Office's basis for the present rejection also states that the specification is "enabling for most of the recited limitations." (Office Action, pg. 3 (emphasis added).) Since the connection between a maintenance dose and a maintenance period is the only issue addressed in the Office Action, Applicants understand that, at the very least, all other recitations in the claims have been found to meet the standards of section 112, first paragraph.

carvedilol for a third or maintenance dose for a maintenance period of greater than six months, as claimed.[2] This alone meets the standards for enablement.

Second, further regarding the Office's concern that the maintenance dose is not directly related to the maintenance period provided in the disclosed clinical trial example, Applicants respectfully submit that the dose titration referred to at column 7, lines 53 to 56 would have been understood by one skilled in the art to result in a maintenance dose, the maintenance phase for administration of which is expressly recited to have "ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study." ('821 patent, col. 7, ln. 53-59.) In other words, one of ordinary skill in the art would have understood a direct relationship between a maintenance dose and maintenance period. The connection between the maintenance dose and the maintenance period is, in fact, provided throughout the specification. Thus, the specification as a whole, including the specific support discussed further below, would have enabled a person skilled in the art to practice a method that includes administering "[the] third dosages each comprising carvedilol [for a] maintenance period . . . greater than six months. . .," as more specifically set forth in the claims.

In support of this understanding, Applicants note the abundance of disclosure related to administering carvedilol according to a three-stage dosing or titration regimen,

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[2] Applicants would likewise traverse a written description rejection under section 112, first paragraph where "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." MPEP § 2163 (*citing Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991)). For example, given the undisputed disclosure of both a maintenance dose and a maintenance period, one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention.

to achieve a 100% or maintenance dose that is administered for a maintenance period.

For example:

> Compounds having the above-mentioned dual properties [(dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists)] are preferably administered flowing a three-stage application scheme. This scheme is characterized by the fact that incremental dosages of the active ingredient are administered to patients over a certain period of time, until the regular maintenance dosage is received. If this maintenance dosage is defined as the setting value being 100%, it was found that the application regimen in a first phase should extend for a period of 7-28 days, whereby only 10-30% of the setting dose are administered. Following this phase, a second application regimen should follow, wherein a dosage of 20-70% of the setting dose is administered to the patient for a period of 7-28 days. After termination of this [second] phase, the third application period follows, wherein the daily complete setting dose (maintenance dose) is administered. The daily maintenance dose can vary between 10-100 mg of said active ingredient.

('821 patent, col. 5, ln. 19-35 (emphasis added).) As one specific example, discussed further below, the first dose can be 3.125 or 6.25 mg per unit dose, the second dose can be 12.5 mg per unit dose, and the third or maintenance dose can be 25 or 50 mg per unit dose. (*E.g.,* '821 patent, col. 6, ln. 6-15.)

In more detail, there is, for example, a first or "challenge period" or "low-dose" dosage:

> The patients are titrated with low amounts of carvedilol, with the initial titration dosage being only 10 to 30% of the daily maintenance dose.

('821 patent, abstract);

> The preferred course of treatment is to start the patient on a dosage regimen with formulations which contain either 3.125 or 6.25 mg of active compound per single unit, preferably given twice daily, for 7-28 days.

('821 patent, col. 5, ln. 47-49);

> The present invention relates also to method of treatment for decreasing mortality resulting from congestive heart failure in mammals comprising internally administering to said mammal in need thereof an effective amount of carvedilol according to the following schedule:
>
> (a) a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7-28 days, given once or twice daily.

('821 patent, col. 6, ln. 1-8); and

> During the challenge period, patients received low-dose open-label carvedilol (6.25 mg b.i.d.) for two weeks.

('821 patent, col. 7, ln. 29-51 (emphasis added).)

Next, there is also a second dosage. For example:

> In the event that the patient exhibits medically acceptable tolerance of the compound for two weeks, the dosage is doubled at the end of the two weeks and the patient is maintained at the new, higher dosage for an additional period, preferably to two more weeks, and observed for signs of intolerance.

('821 patent, col. 5, ln. 54-59);

> (b) thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7-28 days, given once or twice daily

('821 patent, col. 6, ln. 9-11); and

> Patients tolerating low-dose carvedilol were then randomized to blinded medication (carvedilol or placebo) with the dose titrated over several weeks in the range of 6.25 to 50 mg b.i.d. (or equivalent level of placebo).

('821 patent, col. 7, ln. 52-56.)

Lastly, there is also a third or "maintenance" dosage. For example:

> This course is continued until the patient is brought to a maintenance dose. The preferred maintenance dose is 25.0 mg of active compound per single unit, preferably given twice daily, for patients having a body weight of up to 85 kg. For patients having a body weight of over 85 kg, the

> maintenance dose is between about 25.0 mg and about 50.0 mg, preferably given twice daily, preferably about 50.0 mg of active compound per single unit, preferably given twice daily.

('821 patent, col. 5, ln. 59-67 (emphasis added));

> (c) finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.

('821 patent, col. 6, ln. 12-14 (emphasis added));

> The patients are titrated with low amounts of carvedilol, with the initial titration dosage being only 10 to 30% of the daily maintenance dose.

('821 patent, abstract); and

> [After titrating over several weeks in the range of 6.25 to 50 mg b.i.d., the] maintenance phase of each study ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study.

('821 patent, col. 7, ln. 52-59 (emphasis added).) Although this last example in the specification does not expressly use both the phrases "maintenance dose" and "maintenance phase," it would have been more than clear from the context and the knowledge of one of ordinary skill in the art that the final dose to which the patient is titrated is the maintenance dose referred to throughout the specification as the end point of the three-stage dose titration. It would have also been clear that this final dose level, the maintenance dose, was provided for the recited maintenance phase.

Based on at least this disclosure, which clearly provides for an at least three-level dosing method and provides for the relative and sequential relationships between the dosages, not to mention the skill in the art, the relationship between the "third" or "maintenance" dosage and the "maintenance phase" or "maintenance period" is more than sufficient to enable a person skilled in the art to practice the invention commensurate in scope with these claims. In view of this relationship, together with

Office's recognition that "[i]n column 5 a maintenance dose is set forth" and "[i]n column 7, lines 56-67 a six to twelve month maintenance period is given" (Office Action, pg. 3), enabling support for the claim as a whole is more than provided.

Reconsideration and withdrawal of the rejections are respectfully requested.

To the extent this rejection is maintained, Applicants specifically request the Office to provide its specific findings and evidence in support of these findings, as required. (*See, e.g.,* MPEP § 2164.04 ("In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . . This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." (citations omitted).) Among other things, it is requested the Office address the factors according to *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), identifying the factors considered relevant and the Office's evidence and reasoning for each of those factors. (MPEP § 2164.01.)

CONCLUSION

Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

If there is any fee due in connection with the filing of this Statement, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: April 11, 2005

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